REMARKS/ARGUMENTS

Applicants address the Examiner's remarks using the paragraph numbering of the office action. Lack of comment on any remark of the Examiner should not be construed as agreement therewith.

¶3. Applicants maintain their previous position.

¶4. Claims 119, 121-125 and 131 continue to stand rejected as allegedly obvious over Selkoe Wong, and Penney.

In the previous response, applicant explained his position that there was not a prima facie case of obviousness. Briefly to recap, there was no reason to replace Wong's use of KLH in animals with a toxoid from a pathogenic bacteria because Penney teaches that Wong was already using the preferred carrier for animal use. The purported switch from KLH to a toxoid from a pathogenic bacterium without any proposal of human use of a 1-7 Aβ fragment, appears to reflect impermissible hindsight reconstruction of the claimed invention. Furthermore, there was insufficient reason to replace Wong's 1-10 fragment with an Aβ 1-7 fragment. Wong's selection of an Aβ1-10 immunogen was based on the limited sequence data of Aβ available at the time, and the artisan would have no reason to confine his choice of antibody to this region when the full and correct sequence of Aβ was known. Furthermore, based on Selkoe comments, a fragment with only 7 amino acids would have appeared to involve an unnecessary risk of more concern than any minor cost saving from synthesizing a slightly shorter peptide, which risk the artisan could have avoided by using a longer fragment as Wong was doing.

Applicants maintain their previous remarks, but begin by discussing two unexpected results of the claimed conjugates vis-a-vis the cited art. The claimed conjugate is an unexpectedly superior agent for human therapeutic administration than the Aβ1-10-KLH-conjugate discussed by Wong. The superiority arises in part because toxoid from a pathogenic bacterium is more suitable for human use whereas KLH is a preferred carrier for animal use (*see* Penney discussed in the last response). Although the advantage of toxoids from pathogenic

bacteria from human use had already been reported by Penney, the advantage of the claimed conjugates is unexpected because the cited art did not teach that the claimed conjugates had any use in humans. Without the insight provided by the present application that the claimed conjugates have a therapeutic use in humans, the claimed conjugates would have appeared disadvantageous relative to those of the art because the art was already using the preferred carrier for animal use. The advantageous property of the claimed conjugates for use in humans vis-a-vis the cited art can only be viewed as unexpected.

The claimed conjugates are also unexpectedly advantageous for therapeutic use relative to Wong's Aβ1-10 fragment because the claimed use of Aβ1-7 preserves three epitopes predominantly responsible for plaque clearing effects, but reduces the likelihood of T-cell mediated side effects. Table 16 in the present application shows three epitope specificities that are particularly effective in clearing amyloid deposits: Aβ1-5, 3-6 and 3-7. The Aβ1-7 fragment can induce all three of these classes of antibodies. Furthermore, Rammensee, Curr. Opin. Immunol., 1995, 7:85-96 (cited as cite no. 928 by the supplemental IDS filed August 29, 2008) reports that T-cell epitopes are normally at least 9 amino acids long. The claimed Aβ1-7 fragment is smaller than this size, whereas the Aβ1-10 fragment of Wong is longer. Accordingly, the Aβ1-7 fragment is likely to be even less susceptible to generating T-cells than Wong's fragment. Post-filing data have shown that T-cell mediated effects can give rise to side effects in a small proportion of patients (Hock, Neuron, 2003, 38: 543-554, cited as cite no. 534 by the supplemental IDS filed February 6, 2007; and, WO 04/069182 at paragraph 0034, cited as cite no. 918 by the supplemental IDS filed August 29, 2008). Accordingly, a reduction in such side effects is a significant unexpected advantage.

The Examiner cites MPEP § 2143 for the proposition that choosing between a finite number of carriers would have been obvious. However, the present facts and circumstances are distinguishable from the case law underlying MPEP § 2143. Both Pfizer (*Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 82 USPQ2d 1321 (Fed. Cir. 2007)) and Alza (*Alza Corp. v. Mylan Laboratories, Inc.*, 461 F.3d 1286, 80 USPQ2d 1001 (Fed. Cir. 2006)) involved selection of auxiliary substances for known therapeutic agents. By contrast, Aβ1-7 was not known to have any therapeutic properties. Thus, the advantage of the claimed conjugates vis-a-

vis the art for human administration can only be viewed as unexpected. Furthermore, as discussed above, the use of Aβ1-7 confers additional advantages beyond the selection of carriers.

The Examiner also cited MPEP § 2123(I) for the proposition that even non-preferred embodiments are to be considered in making determinations of obviousness. Although MPEP § 2123(I) provides that non-preferred embodiments constitute prior art, it does not say that the characterization of one element of a claim as non-preferred is determinative that the claim as a whole is obvious. The cases cited in MPEP § 2123(I) involve unrelated facts and circumstances to the present. Two of the cases (*Upsher-Smith Labs. v. Pamlab, LLC*, 412 F.3d 1319, 75 USPQ2d 1213 (Fed. Cir. 2005); and *Celeritas Technologies Ltd. v. Rockwell International Corp.*, 150 F.3d 1354, 47 USPQ2d 1516 (Fed. Cir. 1998)) involved anticipation, the issue being whether a single reference disclosing an embodiment of an invention characterized as non-preferred still anticipated. The third case (*Merck & Co. v. Biocraft Laboratories*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), *cert. denied,* 493 U.S. 975 (1989)) involved obviousness based on a single reference. The invention in Merck was a combination of a first component and a second component, both of which were known drugs. The prior art reference disclosed that a genus of 10 drugs (comprising the first component) could be combined with another genus of 120 drugs (comprising the second component) for the identical purpose as claimed. Neither the first component, nor the second component, however, was highlighted as a preferred embodiment in the prior art reference. Against this background, the court stated "all disclosures of the prior art, including unpreferred embodiments, must be considered." *Id.* at 807.

Merck is clearly distinguishable on its facts. Merck involves the combination of two drugs from two lists of drugs, the combination having the same use as the individual drugs. Neither of the drugs was highlighted as being either favored or disfavored in the respective lists. Here, the case of alleged obviousness is based on two references. One of the references (Wong) discusses a 1-10 Aβ fragment linked to KLH for use as research reagent in animals. The other reference (Penney) teaches that KLH is the preferred carrier for research use in animals and that toxoids from pathogenic bacteria are preferred for therapeutic use in humans. The case of obviousness is not simply a combination of two similar substances from different lists but the replacement of what would have appeared to have been a more preferred substance with a less

preferred substance as a result of which unexpectedly, the combination confers an improved suitability for human use. The issue is not whether Penney's teaching constitutes prior art, but whether the claimed conjugates would have been obvious in light of such teaching. In applicant's submission, this teaching only serves to reinforce the unexpected result discussed above; namely that the claimed conjugates have an unexpectedly advantageous property relative to the art conjugates of improved suitability for human administration. This property could not have been expected without knowledge that the claimed conjugates had a therapeutic role in humans.

For this reason, as well as the reasons discussed in the previous response, applicant requests the rejection be withdrawn.

¶5. Claims 119-125 and 131-132 stand rejected as allegedly obvious over the combination of Selkoe, Wong and Penney in further view of Restifo. The examiner asserts Restifo teaches using multiple copies of a peptide as an immunogen. However, Restifo adds no teaching to cure the deficiencies of Selkoe, Wong and Penney. Therefore, claims 119-125 and 131-132 would have been nonobvious for at least the same reasons as discussed above.

¶6. Claims 119, 121-124, 131 and 133-138 stand rejected as allegedly obvious over the combination of Selkoe, Wong and Penney in further view of Hancock. The examiner asserts Hancock teaches use of QS21 as an adjuvant. The Examiner asserts it would have been obvious to use QS21 as an adjuvant in view of Hancock's alleged teaching that it is particularly effective in eliciting antibodies.

The distinctions discussed above are equally applicable here.

In addition, in the previous response, applicant explained that Hancock would not have motivated replacement of Freund's adjuvant used by Wong in favor of QS21. In brief, Freund's adjuvant is a potent adjuvant (Penney, sentence bridging cols. 2 and 3) and the most commonly used adjuvant in animals (Harlow and Lane at p. 98, cited in last response). QS21 although indicated to be suitable for use in humans by Hancock and to increase immunogenicity of RSV proteins relative to no adjuvant or alum (Hancock at col. 3, lines 3-6), is not taught by

Hancock to be more potent or even as potent as Freund's adjuvant for use in animals. The Examiner characterizes this position as an argument for lack of expectation of success, which the Examiner dismisses as merely attorney argument. In fact, however, the Examiner is addressing an argument that was never made. Applicant's position was directed to the lack of motivation or other reason to replace Freund's adjuvant with QS21, not the expectation of success were such a replacement to have occurred.

The purported replacement of Freund's adjuvant with QS21 is in some ways analogous to the purported replacement of KLH with a toxoid from a pathogenic bacteria. The replacement of Freund's adjuvant with QS21 confers an unexpected benefit for use in humans but at a cost of foregoing the most commonly used adjuvant in animals. The benefit in humans is unexpected because Aβ1-7 was not known to have any therapeutic use in humans, as discussed previously.

Although MPEP § 2123(I) provides that non-preferred embodiments constitute prior art, it does not say that the characterization of one element of a claim as non-preferred is determinative that the claim as a whole is obvious. Furthermore, with respect to MPEP § 2144.06, Freund's adjuvant and QS21 are not recognized as equivalents in the art of record. Freund's adjuvant is a potent adjuvant and the most commonly used adjuvant used in animals but restricted to use in animals (Penney paragraph bridging cols. 2-3). QS21 is reported to be suitable for use in humans but of unknown relative potency relative to Freund's adjuvant for use in animals.

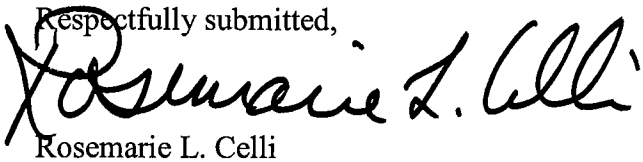
Because the present claims confer an advantage not shared by the art (*i.e.*, suitability for use in humans), which could not have been appreciated absent recognition of a therapeutic role for Aβ1-7, and for the reasons discussed in the previous response, it is submitted that the rejection should be withdrawn.

¶7. Claims 119, 121-131 and 133-143 stand rejected as allegedly obvious over the combination of Selkoe, Wong, Penney and Hancock in further view of Collier. The examiner asserts Collier teaches using vectors for production of diphtheria toxoids and teaches that the vectors can be used for construction of fusion proteins between a diphtheria toxoid and an

antigen. However, Collier adds no teaching to cure the deficiencies of Selkoe, Wong, Penney and Hancock. Therefore, claims 119, 121-131 and 133-143 would have been nonobvious for at least the same reasons as discussed above.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,



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